

REMARKS

Constructive Election

Applicant thanks the Examiner for pointing out on p. 2, para. 1-2 of the Office Action of June 1, 2004 (the "Office Action") that claims 1-7 and 17-47 were improperly cancelled in the submission of February 17, 2004 because the request was in the Remarks Section and not in the Claims Section and the cancelled claims were still written in the claims list, and for pointing out that claims 1-16 and 18-69 are therefore pending. Therefore, Applicant re-asserts that claims 1-7 and 17-47 are cancelled, as indicated in the Amendments to the Claims Section which begins on p. 2 of this paper. Thus, claims 1-7 and 17-47 are no longer included in full in the listing of claims, but are properly listed as cancelled, with no text.

In addition, the Office Action states on p. 2, para. 3-4 that newly submitted claims 49, 50, 53, 54, 56-59, 61-64 and 66-69 are directed to an independent and distinct invention from that originally claimed, and later on p.3 that "Accordingly, claims 49, 50, 53, 54, 56-59, 61-64 and 66-69 are withdrawn from consideration." After a telephone conference with the Examiner on September 7, 2004 it is confirmed that a constructive election of claims 48, 51, 52, 55, 60 and 65 has been made by the Examiner.

Applicant acknowledges the constructive election. However, claims 48, 55, and 60, which claim directed differentiation into ectodermal (48), endodermal (55) and mesodermal (60) cells, respectively, are all encompassed by original generic claim 8, directed to a method for directing differentiation into a specific cell type (i.e., ectodermal, endodermal, or mesodermal). Therefore, all claims which depend from 8, 48, 55 and 60 (including claims 49-54, 55-59, 56-59, 61-69 that have been withdrawn from consideration by the Examiner) should also be allowable if the base generic claim from which they depend is found allowable.

Amendments to the Claims

Claims 8, 48, 55, and 60 are amended to delete the phrase "for differentiating in the presence of at least one exogenous factor" because the Examiner deems this to be a "use" and not a true limitation, and a new step (c) that requires "exposing said dissociated

embryonic cells ... to at least one exogenous factor” is added, to address this concern. Claims 8, 48, 55, and 60 are also amended to insert the word “dissociated” before embryonic cells in steps (b) and (c), to distinguish the “dissociated” embryonic cells in (b) and (c) from the original embryonic stem cells in step (a).

Claim 10 is also amended to insert “dissociated” before “embryonic cells,” to distinguish the embryonic cells of the monolayer from the original embryonic stem cells in step (a) of claim 8 that form embryoid bodies.

Claims 50, 52, 54, 57, 59, 62, 67, and 69 are amended to replace “dissociating” with “exposing” in step (c), to provide a proper antecedent basis for the reference to “exogenous factor” in each of these claims.

Applicant hereby submits that these amendments do not add new matter, and that support for these limitations is found in the original claims and in the specification in Examples 1 and 2.

Claim Rejections under 35. U.S.C. § 112, para. 1 – Enablement

The Examiner states that “The human embryonic cells *derived from EB’s* require the presence of an extracellular matrix or feeder cells to remain undifferentiated.” See Office Action, p. 3, last para., emphasis added. However, claim 8 is directed to a “method of directing differentiation of human embryonic cells to a specific cell type that comprises ...permitting a population of human embryonic stem cells to form embryoid bodies *in vitro*; [and] dissociating the embryoid bodies to provide embryonic cells” among other steps. Although extracellular matrix is required by Thomson et al., and disclosed in Example 1, this is merely a preferred embodiment and method for providing human embryonic cells from EBs, but the applicants should not be limited to just the preferred embodiment.

Dr. Benvenisty has successfully cultured human embryonic cells in the absence of extracellular matrix, contrary to the teachings of Thomson et al. According to Dr. Benvenisty, “claim 10, which depends from claim 8, is fully enabled because although Example 1 describes culturing of embryoid bodies (EB)-derived embryonic cells in the presence of fibronectin, I have also successfully cultured said embryonic cells in the presence of gelatin instead. Gelatin is not extracellular matrix (ECM) and, therefore,

embryonic stem cells may be cultured in the absence of ECM. Example 1, and the methodology of Thomson et al. is a preferred way of culturing embryonic cells derived from EBs, but those skilled in the art would understand that other ways are also possible.” See Declaration of Dr. Benvenisty, para. 3.

Claim 10 also limits the human embryonic cells of claim 8 to “monolayer cultures” and is herein amended to insert the word “dissociated” before “embryonic cells” to distinguish that it is the embryonic cells derived from EBs that are monolayer cultures. On this point, the Office Action further states that “It is unclear that embryonic cells grown on feeder cells, if applicant has support for such a limitation, would be considered a monolayer.” See Office Action, p. 4, lines 2-3. First, support for such a limitation is found in the specification on p. 13, lines 29-31 (“Human embryonic stem cells were grown on a feeder layer of mouse embryonic fibroblasts (MEF)...” see *supra*). Second, the specification states on p. 13, line 29 through p. 14, line 1, that the human ES cells were transferred to a gelatin coated plate and “cultured further” after growing them on a feeder layer of mouse fibroblasts, and further states that “After 5 days, the EBs become dissociated and cells are cultured *as a monolayer* forming differentiated embryonic (DE) cells. This protocol allows for initial differentiation ... and further differentiation *as a monolayer* wherein cells can be exposed to exogenous growth factors.” Emphasis added. And finally, as amended, claim 10 distinguishes the embryonic cells of the monolayer as the dissociated embryonic cells of claim 8. As shown above, the specification on p. 13, line 29 through p. 14, line 1 clearly provides support for dissociated human embryonic cells cultured as a monolayer.

Applicant appreciates the Examiner’s concern with the dichotomy presented by Thomson et al. who require extracellular matrix to grow ES cells to maintain undifferentiated cells, and the disclosure and claims for the instant application which do not require extracellular matrix for the growth of hES derived from EBs. However, merely because the Thomson et al. protocol requires extracellular matrix does not mean that the initial paragraph and protocol of Example 1 is not enabling as an alternative protocol, given that other references available in the art and the attested experiences of Dr. Benvenisty can be coupled with the disclosure to support enablement. For the above

reasons, Applicant respectfully submits that claims 8 and 10 are enabled and therefore requests withdrawal of the enablement rejection under 35 USC § 112, para. 1.

Claim Rejections under 35. U.S.C. § 103(a) – Obviousness

The Examiner has rejected claims 8, 9, 11, 12, 60 and 65 as being unpatentable over Thomson et al. (1998) *Science* **282**, 1145-1147 in view of Shambloott et al. (1998) *PNAS (USA)* **95**, 13726-13731 and further in view of Yuen et al. (1998) *Blood* **91**, 3202-3209. As the foundation for this rejection, the Office Action states on p. 4 that “Thomson teaches human ES cells that retain the ability to form all three embryonic germ layers.” In fact, this is not what Thomson et al. teaches. According to Dr. Benvenisty, “Although Thomson affirms that the human ES cell lines that were generated “maintained the potential to form derivatives of all three embryonic germ layers” (see Thomson, p. 1146, 1st column, lines 30-32), this potential was evidenced in the form of teratomas generated in SCID mice injected with said cell lines (*id.*, p. 1147, Figure 4).” See Declaration, para. 4.

Applicant believes that the Examiner is confused about the teachings of Thomson et al. and has consequently dismissed the distinctions between Thomson et al. and the presently claimed subject matter. ES cells can be tumorigenic if injected into SCID mice, as shown by Thomson, but that does not mean that this is the only and most prominent results and feature - otherwise all pregnancies would end in a tumor and not in a healthy baby.

Directing the differentiation of human embryonic cells *in vitro*, as detailed in the presently claimed invention, and having the cells differentiate *in vivo* inside a host, as shown by Thomson et al., are completely different. The results obtained are different, which emphasizes that the ES cell line obtained by Thomson et al. is not what is described in the present invention. To the contrary, it reinforces Reubinooff's position that human EBs cannot be obtained from hES cells. Thomson is also an acknowledged expert in the field of stem cell research, and like many others, was also trying to develop the formation of human EBs and subsequent differentiation of the EB-derived human ES cells himself, but did not succeed. Negative results are not publishable in science, so

Thomson published an article on what he succeeded in doing, which was to generate teratomas.

Teratomas are tumors, i.e. cells growing abnormally and uncontrollably, often in an undifferentiated state. The present application claims a “method for *directing differentiation* of human ES cells to a specific cell type” (see claim 8) and a method wherein “said embryonic cells form human brain cells” (see claim 51), among other things. As explained by Dr. Benvenisty, “the problem that we are trying to solve in our laboratory is the development of human stem cell-derived differentiated cell lines that can eventually be used as material for transplantation.” *Id.* Therefore, Thomson et al. is not appropriate as the core reference in an obviousness rejection because Thomson et al. defeats the intended purpose of and thus teaches away from the presently claimed invention.

Thomson et al. is even more problematic as the basis for the obviousness rejections because, as noted by Dr. Benvenisty, “Thomson’s results do not point to the generation of differentiated cell lines of the three germ cell layers but rather, to the generation of tumor cells that display markers of the three embryonic germ layers, which is what characterizes these tumor cells. These are not directly differentiated embryonic cells to a specific cell type, but rather embryonic stem cell-derived cell lines that form a tumor, and clearly would not be suitable for transplantation.” Declaration, para. 5. Thomson et al., the key reference for the obviousness rejections, teaches an ES cell line that forms teratomas, are not capable of having differentiation directed, and thus are not suitable for transplantation, and so Thomson et al. actually teaches away from the presently claimed invention.

The Examiner asserts (and assumes) that Thomson et al. teaches that human ES cells retain the ability to form all three embryonic germ layers, but this assumption is not shared by those skilled in the art. As stated by Dr. Benvenisty, “the only two molecular markers evaluated in Thomson’s cell lines were human chorionic gonadotropin (HCG) and alpha-fetoprotein (AFP), which are also markers for extra-embryonic cells. HCG is expressed in trophoectoderm, while AFP is expressed in the yolk sac, both part of the extra-embryonic tissues. Therefore, besides the formation of teratomas, Thomson did not

unequivocally prove the generation of differentiated cell lines of the three different germ layers.” See Declaration, para. 6.

Regarding the other two references that the Office Action has combined with Thomson et al. to support the obviousness rejection of claims 8, 9, 11, 12, 60 and 65, Shamblott et al. teaches production of hEBs from human primordial *germ* cells and Yuen et al. teaches the production of EBs in suspension from *mouse* ES cells, not human ES cells. As clearly explained by Dr. Benvenisty, “[h]uman EG cells are very different from hES cells” and “any cell line deriving from hEG cells will be dissimilar from cell lines derived from hES cells.” See Declaration, para. 7-8.

As summarized in a table in the Declaration, not only is the origin of hEG cells different from that of hES cells, hEG cells cannot be imprinted *de novo*, and they cannot survive passage more than about 20 times. See Declaration, table, para. 7. And even though some cell lines, like those disclosed in Shamblott et al., exhibit some pluripotency properties such as the ability to form embryoid-like bodies, as pointed out by Dr. Benvenisty, “[i]t is a well known fact to those skilled in the art that ES cells have an inherent pluripotency that is not reproducible by any other cell line.” See Declaration, para. 8. Furthermore, Dr. Benvenisty cautions that just because the cell line disclosed in Shamblott et al. formed embryoid-like bodies, “it is still not correct to say that the embryoid body-*like* structures of Shamblott et al. are equivalent to the embryoid bodies derived from hES cells (see *id.*). Emphasis added.

According to Dr. Benvenisty, although the Shamblott hEG cells may have formed embryoid-like bodies, and although they may have differentiated into all three germ layers, “it cannot be assumed that the Shamblott et al. differentiated cells have the same potential as cells derived from hES cells.” *Id.*

Other shortcomings of the Shamblott et al. cells punch holes in the strength of citing it as a 103(a) reference. As mentioned briefly above, unlike the hES cells of the instant application, the hEG cells in Shamblott et al. are already imprinted and cannot be imprinted *de novo*, and the Shamblott et al. hEG cells cannot survive being passaged more than about 20 times. In addition, the Shamblott et al. hEG cells undergo spontaneous differentiation, which completely teaches away from the presently claimed invention, which requires directed differentiation. See Declaration, para. 9, generally.

Therefore, as emphasized by Dr. Benvenisty, “at every critical level it is fundamentally incorrect to consider the Shamblott et al. differentiated cells as equivalent to the EB-derived differentiated ES cells of the present invention. Unlike the cells produced in our laboratory, the Shamblott et al. cells cannot be imprinted *de novo*, they spontaneously differentiate and so cannot be directed to differentiate when required, and they cannot survive after more than 20 passages.” See Declaration, para. 10.

Regarding Yuen et al., the Examiner posits that Yuen et al. teaches the production of mouse embryoid bodies in suspension from mouse ES cells, and then dissociated and exposed to exogenous factor to direct differentiation into primitive erythroid cells. See Office Action, p. 5. But so what? In a field as unpredictable as stem cell research, showing directed differentiation of mouse ES cells that are derived from mouse EBs is not enabling for directed differentiation of human ES cells derived from human EBs, even though in hindsight the protocols are remarkably similar. As explained in MPEP § 2164.03, the Predictability of the Art is closely related to the Enablement requirement. Specifically, “if little is known in the prior art about the nature of the invention, and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling.” While this paragraph discusses the level of detail needed in the specification of the invention, the same standard applies to references being cited for obviousness rejections.

In particular, the Applicant is the first to successfully show how one can direct differentiation in human ES cells derived from human EBs. Moreover, the prior art was extremely unpredictable until the Applicant’s remarkable breakthrough. At the time the presently claimed invention was filed, efforts by persons skilled in the art to show *in vitro* formation of human EBs had failed, and efforts to form EBs from monkey ES cells (Rhesus and marmoset) had proven impossible or sporadic at best, never mind taking it all a step further to direct differentiation of hES cells derived from human EBs.

Dr. Benvenisty stresses that Yuan et al. teach the generation of “a primitive erythroid cell line from *mouse* ES cells, not human ES cells.” See Declaration, para. 11. This distinction cannot be emphasized enough. As explained further, “[a]lthough Yuen et al. mention the formation of EBs, they do not show said EBs, and certainly do not show the presence of EB molecular markers. Scientists working in the field of stem cell

research understand that it does not follow that just because a procedure is successful in mice ES cells that it will be successful in human ES cells.” *Id.*

To establish a *prima facie* case of obviousness three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available in the art, to modify the reference or to combine references. Second, there must be reasonable expectation of success, and third, the prior art reference (or combined references) must teach or suggest all the claim limitations. In the present case, the *prima facie* case fails on two of the three criteria – lack of motivation, and no reasonable expectation of success.

As admonished in MPEP §2145 X. B., “... ‘obvious to try’ is not the standard under 35 USC § 103” Although the majority of those skilled in the art of stem cell research may have been motivated to try to get hES cells to form human EBs, and may have been motivated to continue experimenting to attempt to determine how to direct differentiation of hES cells derived from the EBs so formed, actually determining the experimental conditions to successfully achieve the desired results is not obvious even if everyone is working on the problem.

More importantly, there is no reasonable expectation of success. The knowledge generally available in the art at the time the presently claimed application was filed did not provide evidence that it was possible to form human EBs from human ES cells, let alone provide any indication that it would then be possible to take hES cells derived from those EBs and direct differentiation. Dr. Benvenisty emphasizes that

At the date of the present invention, it was only known in the field of stem cell research that it was possible to obtain EBs from mouse ES cells. However, it was not at all known, neither obvious, nor trivial, to obtain EBs from human ES cells. Reubinoff [Reubinoff et al., (2000) *Nature Biotechnology*, Vol 18, pp. 399-404] described how differentiation of human ES cell *in vitro* did not lead to the formation of embryoid bodies (see p. 401, 1st column, lines 26-29, and 2nd column, lines 1-100). In addition, Thomson [Thomson et al., (1995) *Proc. Natl. Acad. Sci. USA*, Vol. 92, pp. 7844-7848 – see Exhibit B] was unable to show the formation of embryoid bodies in Rhesus monkey cells – which are closer in the evolutionary scale to human cells than marmoset cells, from which only sporadically EBs were formed [Thomson et al., (1996) *Biol. Reprod.*, Vol. 55, pp. 254-259 – see Exhibit C]. Thus, the state of the art at the time of the invention was essentially that the formation of embryoid bodies from human ES

cells, especially based on the technology used for mouse ES cells, was not possible. See Declaration, para. 12

Further, MPEP § 2145, subsection X. A. holds that impermissible hindsight cannot be used to support an obviousness rejection when the knowledge required to modify the cited references to arrive at the claimed invention comes from the Applicant's own disclosure. It is not appropriate for the Examiner to dogmatically hold, contrary to the opinions and publishings of recognized experts at the time, that because something was successful in mouse ES cells that it would have been successful in human ES cells. As asserted by Dr. Benvenisty "[i]t is erroneous to propose that without undue experimentation, it was obvious to combine the teachings of Thomson et al. (2000), Shambloott et al.(1998) and Yuen et al.(1998) and arrive at the present invention. If it was obvious, especially when considering how important the generation of embryoid bodies from human ES cells is for science in general and particularly for medicine, many other laboratories would have published such findings concomitantly. But except for the work in our laboratory, no other laboratory in the world was successful in developing the technology of generating embryoid bodies from human ES cells." See Declaration, para. 13.

And as explained by Dr. Benvenisty, "[i]n a News Focus in Science magazine (Vogel, G., (2002) *Science*, Vol. **295**, pp. 1818-1820 – see Exhibit D) under a section entitled "Fundamental Firsts", my achievements of both embryoid bodies formation and directed differentiation of human ES cells are highlighted." *Id.*, para. 14. And later, in that same article, Dr. Benvenisty "is credited with other firsts, verifying that [he] was first to successfully produce human differentiated ES cells." *Id.* Para. 15

Elsewhere in the Office Action the Examiner rejects claims 8-12, 14-16, 48, 51 and 52 as being unpatentable over Thomson et al. in view of Shambloott et al. and further in view of Bain et al. (1995) *Devel. Biol.* **168**, 342-357 (see Office Action, p. 6); rejects claims 8, 11, 13, 48, 51 and 52 as being unpatentable over Thomson et al. in view of Shambloott et al. and further in view of Bain et al. and Wobus et al. (1988) *Biomed. Biochim. Acta* **47**, 965-973 (see Office Action, p. 7); and rejects claim 55 as being unpatentable over Thomson et al. in view of Shambloott et al. and further in view of Bain et al. and Wobus et al. (see Office Action, p. 9).

The failings of Thomson et al. in combination with Shamlott et al. have been described above in detail. According to Dr. Benvenisty “Bain reports the treatment of mouse ES cell-derived embryoid bodies with retinoic acid (RA) and their differentiation into the neuronal lineage. The technology of developing embryoid bodies from mouse ES cells and directing their differentiation was known and established at the time of the present invention. However, the techniques and protocols that applied for mouse ES cells were not adequate for human ES cells. Therefore, the establishment of embryoid bodies from human ES cells may be considered a new and not obvious technology, since it was developed at a time when all the research reported that such technology was not possible (Reubinoff et al, 2000).” See Declaration, para. 18.

And regarding combinations with Wobus et al., Dr. Benvenisty summarizes the teachings of Wobus et al. by stating that similar to other cited references “Wobus et al. report the effect of nerve growth factor (NGF) on the differentiation pattern of mouse ES and embryocarcinoma cells (EC) cells, and showed nerve cells differentiation. However, the techniques and protocols that applied for mouse ES cells were not adequate for human ES cells.” See Declaration, para. 22.

As argued above, the *prima facie* case of obviousness fails for lack of motivation or suggestion to combine or modify the cited references to arrive at the presently claimed invention, and especially fails for lack of a reasonable expectation of success. The Examiner has cited a multitude of combinations to attempt to establish a *prima facie* case of obviousness against the presently claimed invention, but the combinations do not hold up. Without the impermissible use of hindsight, one skilled in the art would not find the suggestion to combine and/or modify the teachings in the prior art of stem cell research – a hugely unpredictable field as attested to by Dr. Benvenisty and other experts in the field, Reubinoff among them – to solve the problem of translating results in mice and monkeys to humans such that not only did human EBs form from human ES cells, but that hES cells derived from those human EBs could be directed, at will, to differentiate.

Finally, Dr. Benvenisty, an acknowledged expert in the area of stem cell research, disagrees with the statements in the Office Action regarding what the teachings of Reubinoff stand for. According to Dr. Benvenisty, “[t]he main issue at stake in the present invention is the generation of differentiated cells from embryoid bodies from

human ES cells. At the time of the present invention, as stated by Reubinoff (2000), “manipulations used in our laboratory and elsewhere to facilitate embryoid body formation and multilineage differentiation of mouse ES cells induced the death of human ES cells” (Reubinoff et al. Nature Biotech., Vol. 18, p. 401 2nd column, lines 7-10) and therefore, it was not obvious to produce differentiated cells from human EB’s.” See Declaration, para. 23.

And regarding the Examiner’s discussion of the Reubinoff results based on high density versus low density (smaller clumps of cells) or single cells, as explained by Dr. Benvenisty, “the present application uses semi-confluent cultures, which to a person skilled in the art means high-density cultures.” See Declaration, para. 24. Further, Dr. Benvenisty makes clear that “it should be noted that it is unlikely that the reason why Reubinoff did not succeed in generating human ES cell-derived embryoid bodies was the number of cells used. The present invention also makes use of semi-confluent cultures which are essentially high density cultures. Reubinoff did not use single cells because it is not possible (or rather, to this day there are no reports) to generate EBs from single cells.” *Id.*.

Reubinoff, an acknowledged expert in the area of stem cell research, states that the parallel experiments in mice do not work. Dr. Benvenisty, another acknowledged expert in the field of stem cell research also attests in his Declaration that it was not possible to successfully translate the mice experiments known at the time the present application was filed to human ES cells, even with all the knowledge in the field available and even with numerous laboratories attempting to do that very thing. Contrary to leading experts in the area of stem cell research, giving Dr. Benvenisty credit for being the first to successfully induce formation of human EBs from human ES cells, the Examiner continues to assert that because something worked in mice it would have worked in humans for anyone who had bothered to try.

What is novel and non-obvious about the presently claimed invention is the idea that one can direct differentiation of human ES cells from human EBs using exogenous factors. Professor Benvenisty was the first one to succeed in human ES cells. In fact, when Dr. Benvenisty “attended a conference in 2001 and presented [his] results showing human embryoid body formation from human ES cells and subsequent directed

differentiation of the human embryonic cells, and many experts in the field simply did not believe [him], including Reubinoff, questioning [his] results intensely.” Such an important step forward in the field of human embryonic stem cell research cannot be considered obvious (*see id.*)

Before Dr. Benvenisty’s laboratory was able to get human ES cells to form EBs, and was then able to direct the differentiation of hES cells derived from those EBs, many other world-class laboratories had attempted to use what was known in mouse stem cell research with human ES cells and all had failed. Yet in one single sentence (“These arguments are not persuasive.”) the Examiner discounts all of Dr. Benvenisty’s considerable expertise and that of others acknowledged to be experts in the field and asserts that if it worked in mice it will work in humans. Having the hindsight of Dr. Benvenisty’s success does not take away from the difficulty in achieving that success, the non-obvious nature of that success, nor make the Examiner’s assertion that the effort was obvious true. The whole world may have been motivated to try to get the mouse experiments with stem cells to work in human stem cells. But no one had the motivation to modify the many references dealing with monkey and mouse stem cells to arrive at the unique solution found in Dr. Benvenisty’s laboratory that ultimately was successful at forming human EBs from hES cells, and then discovering a way to direct, at will, the differentiation human ES cells derived from human EBs. In short, no one succeeded at the acknowledged goal until Dr. Benvenisty’s laboratory showed the way.

For all the foregoing reasons, Applicant respectfully submits that the pending claims are not obvious in light of the cited prior art. Reconsideration of the claims and withdrawal of the obviousness rejections are therefore requested.

CONCLUSION

Claims 1 – 7, 17 – 47, and 49, 50, 53, 54, 56-59, 61-64 and 66-69 are withdrawn without prejudice, but Applicant reserves the right to pursue such claims in a later related application.

In view of the arguments and amendments presented, Applicant respectfully submits that all pending claims are now in condition for allowance. Reconsideration of the claims and a notice of allowance are therefore respectfully requested.

Applicant believes that only a one-month extension of time is required and submits a petition for a one-month extension with this response along with a check for \$55 to cover the Extension Fee. In the event that an additional extension is required, however, this conditional petition for a further additional extension of time is requested. If any additional fees are required for the timely consideration of this application, please charge deposit account number 19-4972.

Dated: September 21, 2004

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Barbara J. Carter". The signature is fluid and cursive, with the first name "Barbara" and last name "Carter" clearly distinguishable.

Barbara J. Carter
Registration No. 52,703
Attorney for Applicant
Bromberg & Sunstein LLP
125 Summer Street
Boston, MA 02110-1618
(617) 443-9292

01822/00113 333295.1